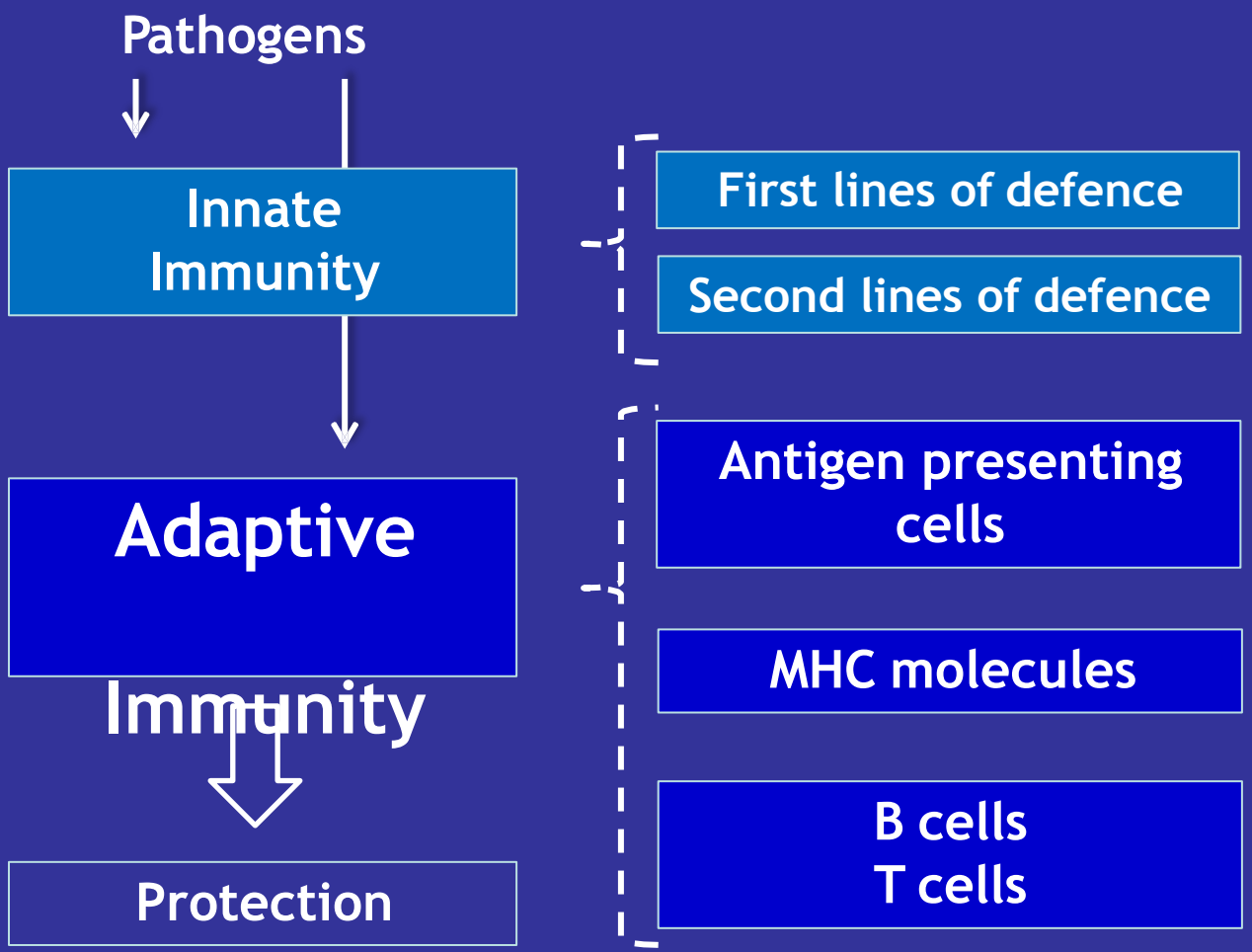
Adaptive immunity

Concept of immune response

A collective and coordinated response to the introduction of foreign substances in an individual mediated by the cells and molecules in the immune system.

Goal of the lecture



Comparison between Innate and Adaptive Immunity

Attribute	Innate Immunity	Adaptive Immunity
Activation	Active prior to exposure to any microbe or antigen	Activated by exposure to microbes or antigens
Lag phase	Absent Response is immediate	Present Response takes few days
Specificity	Limited Targets all pathogens	High Targets specific pathogen
Memory	Absent Same response in 1st and subsequent exposure	Present Amplified response in subsequent exposure

Adaptive Immunity

Adaptive immune system has two arms

Adaptive Immunity

Humoral Immunity	Cell mediated Immunity
1-Provided byT& or B lymphocytes	1.Provided by T lymphocytes
2-Can recognize protein, polysaccharide, phospholipid and nucleic acid antigens	2.Can recognize only protein antigens
3-Can act against soluble or free antigens by class II MHC molecules	3.Recognizes antigens presented by APCs with Class I or Class II MHC molecule
4-Provides immunity to extracellular bacteria, viruses and toxins	4.Provides immunity to intracellular bacteria, viruses, fungi and protozoa
5-Causes Type I, II & III hypersensitivity	5.Causes Type IV hypersensitivity Causes acute graft rejection

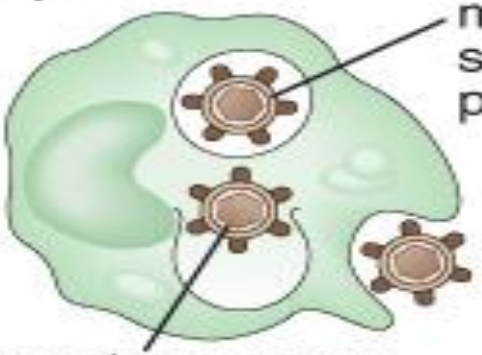
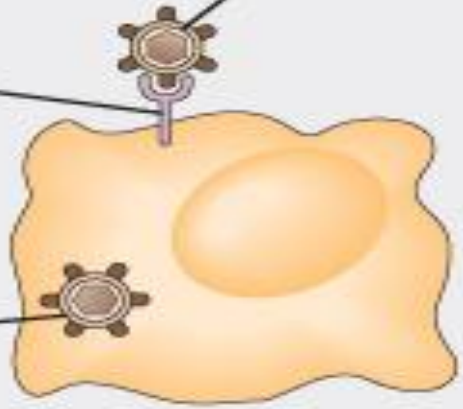
Adaptive immunity

Adaptive immunity response mediated by :

1- antibody to eliminate extra cellular pathogen (humeral immunity).

2- cell-mediated immunity for intracellular pathogen which required T-cell .

Types of intracellular microbes combated by T cell-mediated immunity

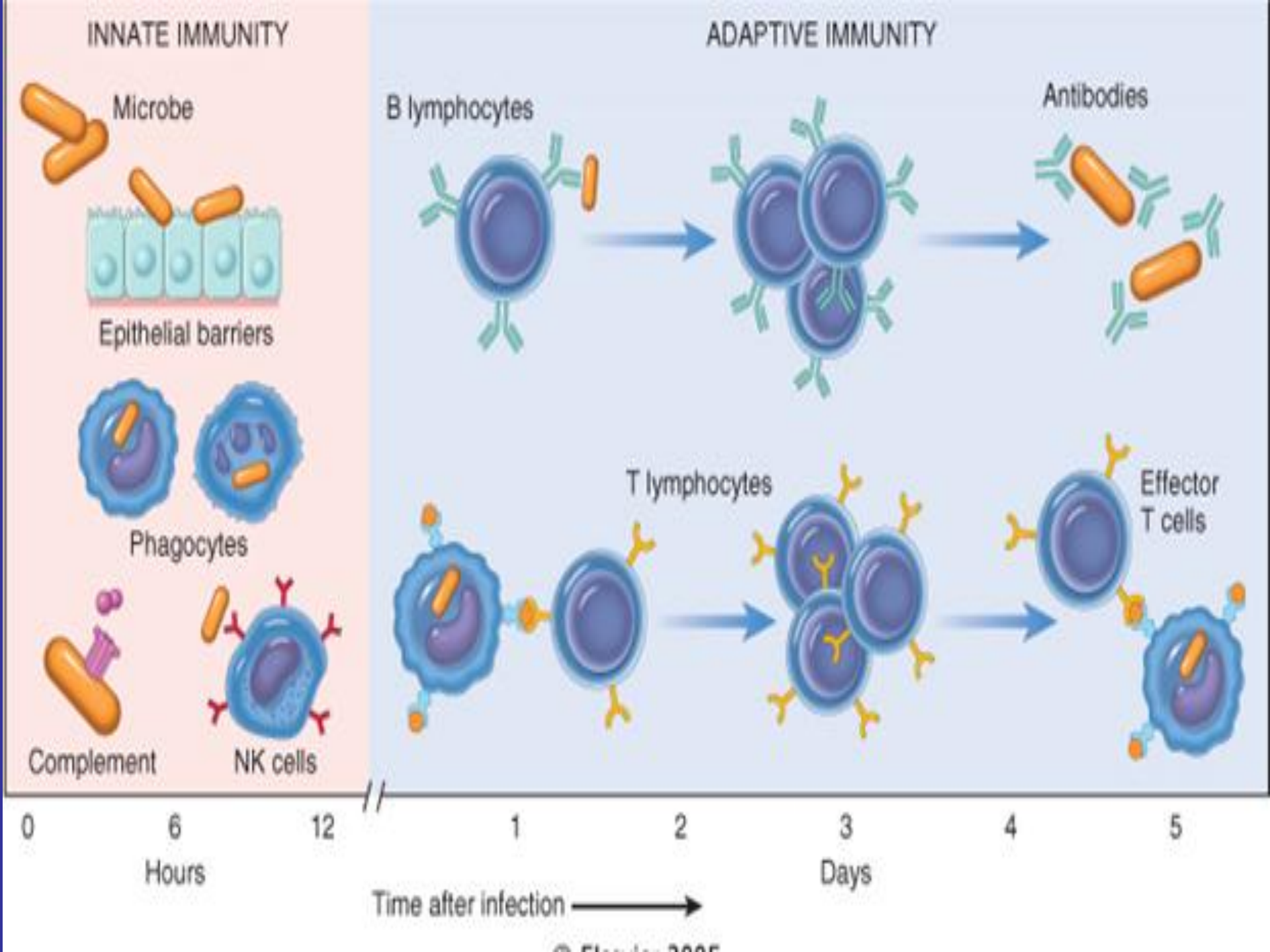
Intracellular microbes	Examples
A Phagocyte  Phagocytosed microbes that survive within phagolysosomes Microbes that escape from phagolysosomes into cytoplasm	Intracellular bacteria: Mycobacteria *Listeria monocytogenes* *Legionella pneumophila* Fungi: *Cryptococcus neoformans* Protozoa: *Leishmania* *Trypanosoma cruzi*
B Nonphagocytic cell (e.g. epithelial cell)  Virus Cellular receptor for virus Microbes that infect nonphagocytic cells	Viruses: All Rickettsiae: All Protozoa: *Plasmodium falciparum* *Cryptosporidium parvum*

Adaptive immunity

Adaptive immunity acquired by two ways:

a- passive : Transmitted by antibody or T-cell pre-formed in another host .

b- active : induced after contact with Ag (clinical and sub clinical infection , immunization with live or killed microbes or microbial product).


INNATE IMMUNITY
ADAPTIVE IMMUNITY
Microbe
Epithelial barriers
Phagocytes
Complement
NK cells
B lymphocytes
Antibodies
T lymphocytes
Effector T cells
0
6
12
1
2
3
4
5
Hours
Days
Time after infection

Different types of antigen-presenting cells

Name	Location	Present to
Dendritic cells	Lymph nodes Mucous Membranes Blood	T cells B cells
Langerhans' cells	Skin	T cells
Macrophages	Various tissues	T cells
B cells (BCR)	Lymphoid tissues	T cells

Features of Antigen Presenting Cells

- **Strategic location**
  - Skin (SALT)
  - Mucous membranes (GALT, NALT, BALT)
  - Lymphoid organs (Lymph nodes, spleen)
  - Blood circulation (plasmacytoid and myeloid DC)
- **Pathogen capture**

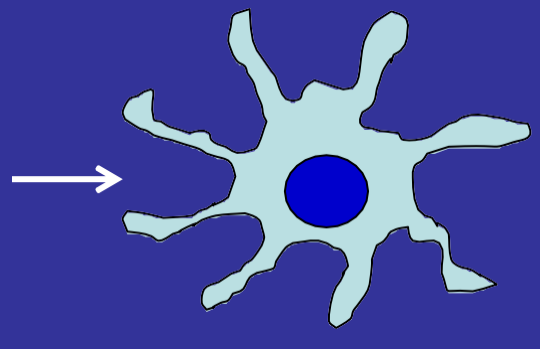
  -Phagocytosis (whole microbe)

  -Macropinocytosis (soluble particles)cell drinking
- **Diversity in pathogen sensors (PRRs)toll like R**
  - Extracellular pathogens (bacteria)
  - Intracellular pathogens (viruses)

Features of Antigen-presenting cells

Capture/processing/presentation

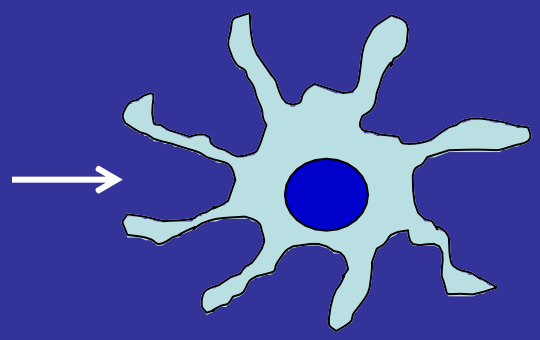
Extracellular Microbes - PAMPS



Humoral Immunity
Antibodies
Complement

Antigen presentation by Major Histocompatibility Complex (MHC)

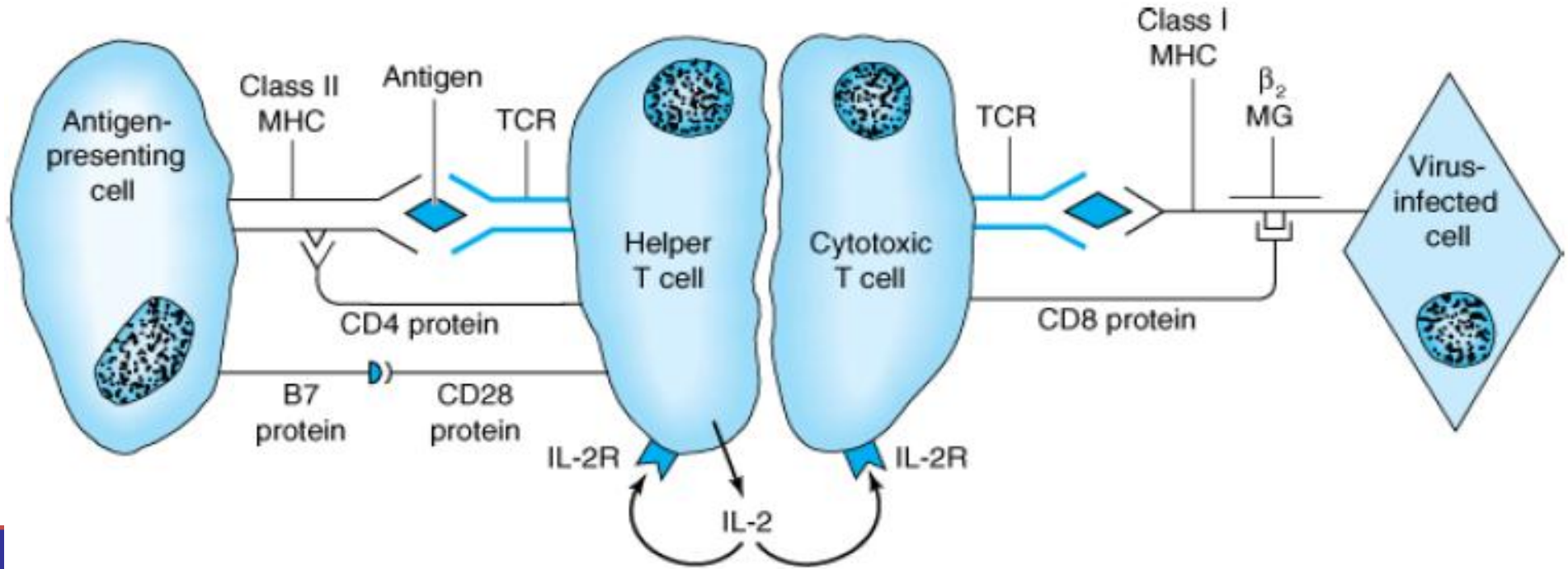
Intracellular Microbes PAMPS -

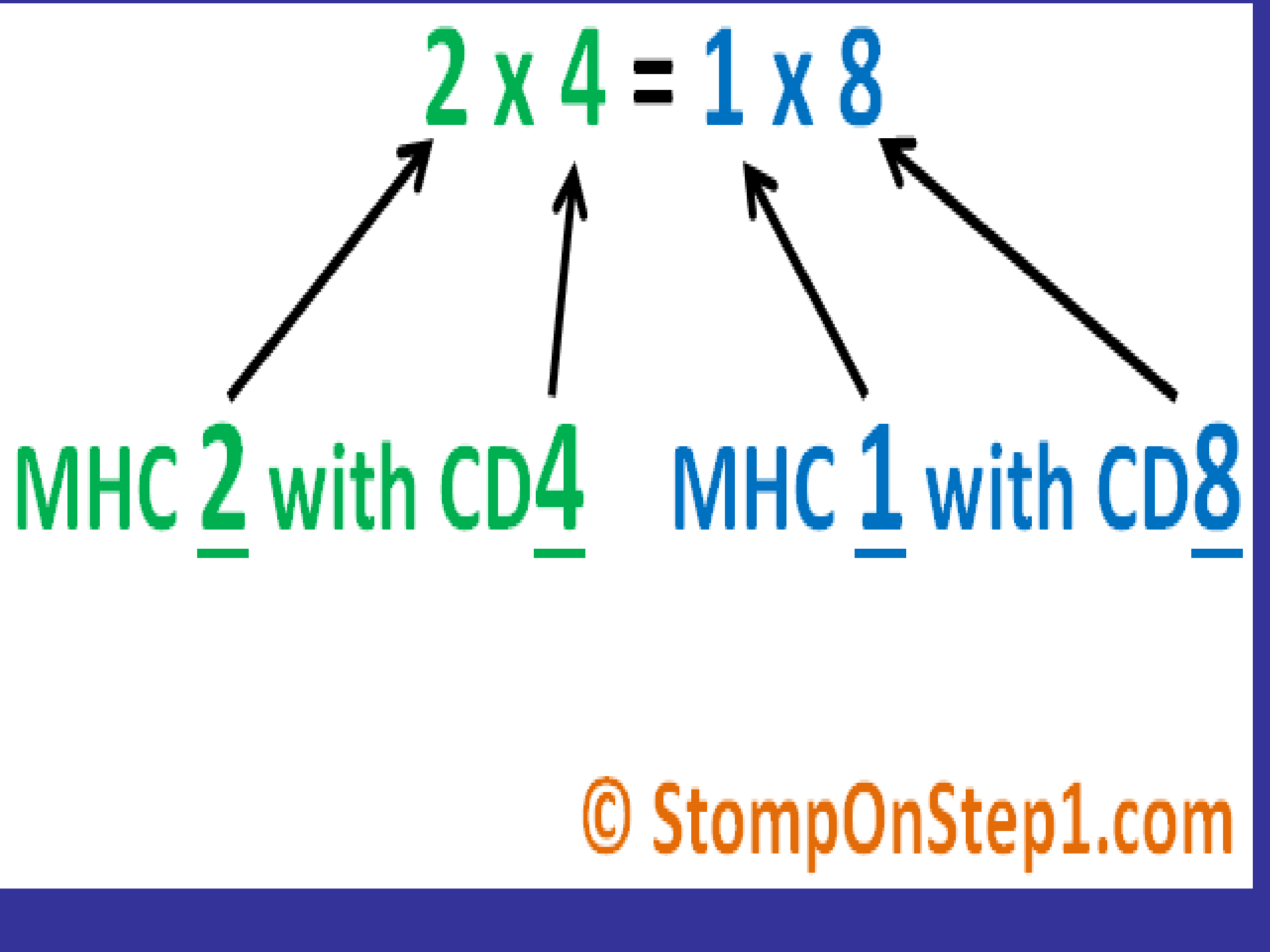


Cell-dependent immunity
Cytotoxic T cells
Macrophages
Antibodies

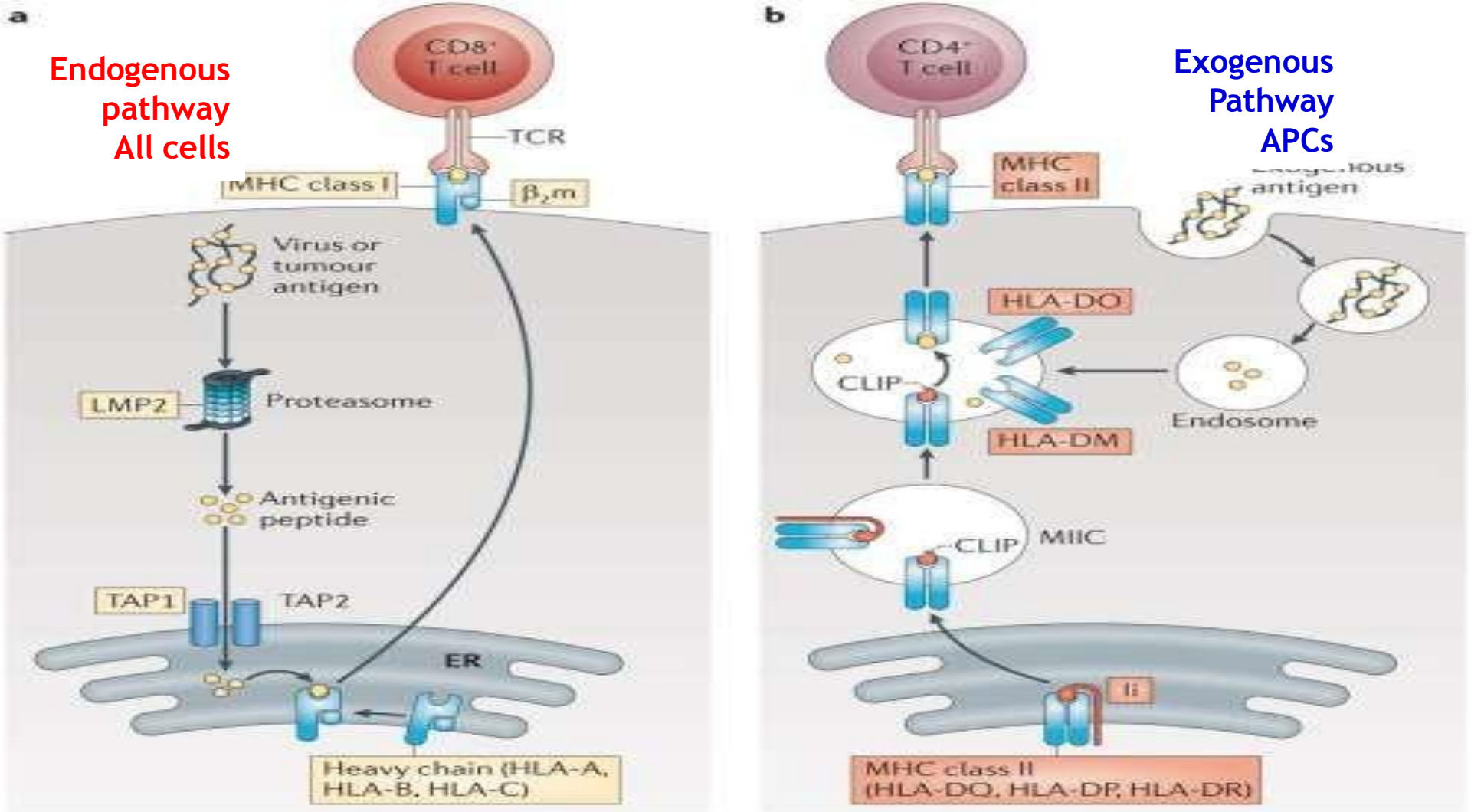
MHC Restriction

T cells (CD4 helper) recognize antigen in association with class II MHC proteins, whereas (CD8 cytotoxic T cells) recognize antigen in association with class I MHC proteins. This is called MHC restriction; {Rule of8}




2 x 4 = 1 x 8
MHC 2 with CD4
MHC 1 with CD8
© StompOnStep1.com

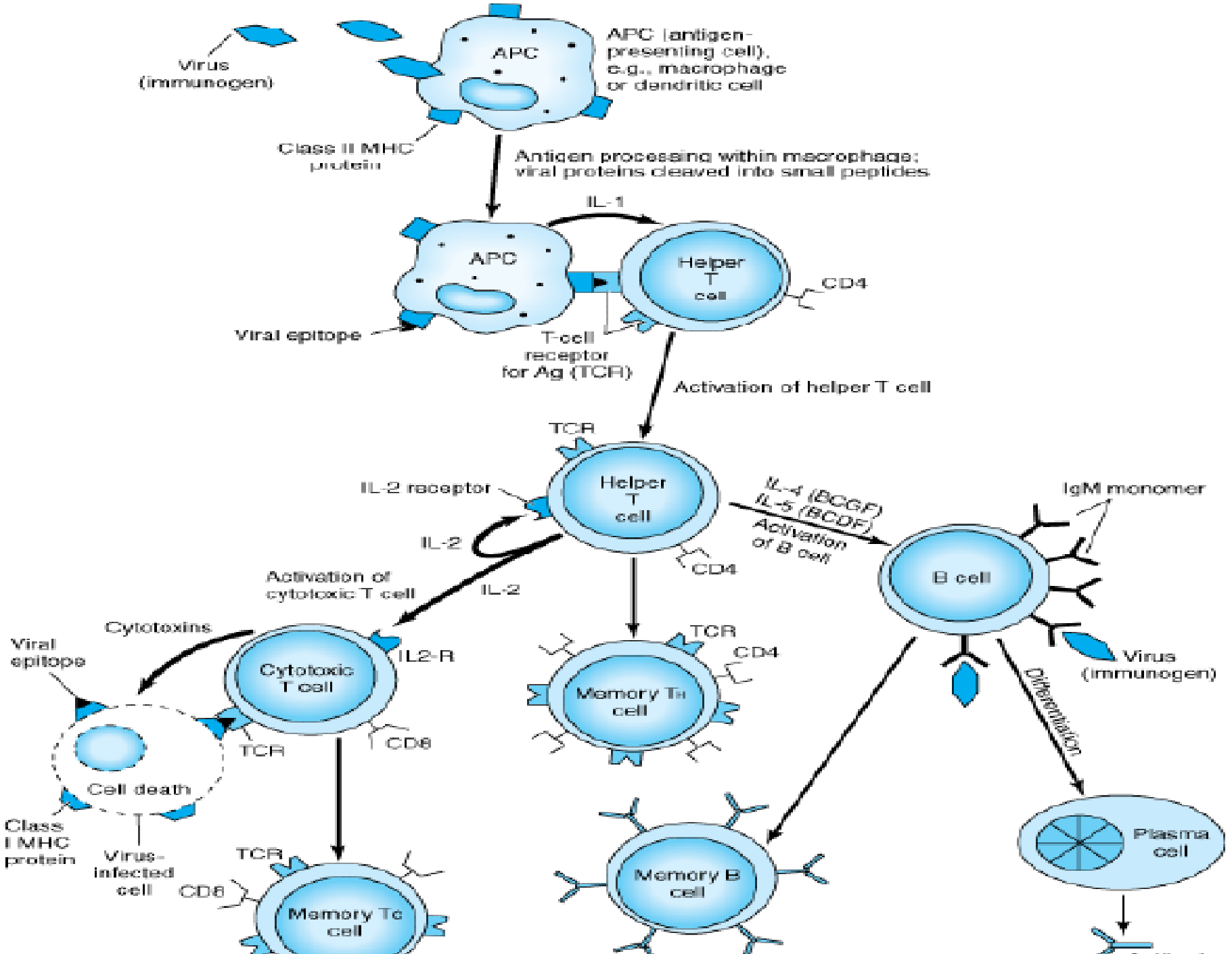
Antigen processing and presentation pathways



Nature Reviews | Immunology

Antigen capture , processing and presentation :

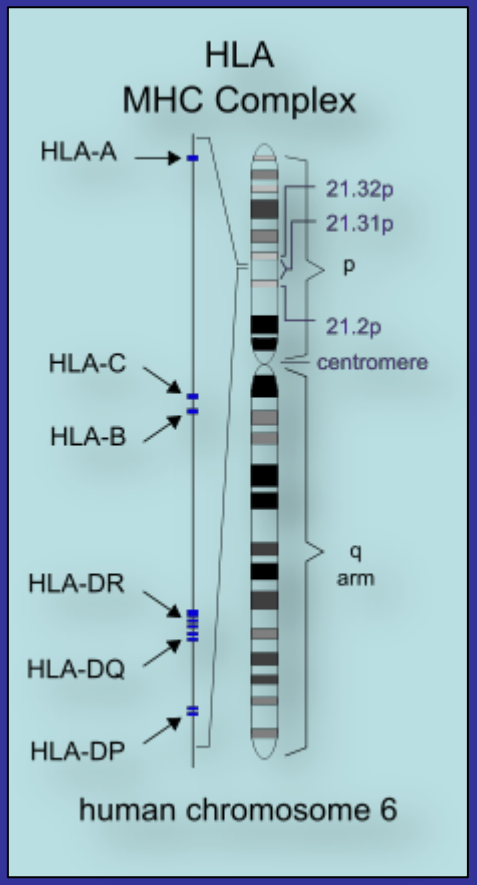
- Endogenous antigens within cells (like intracellular viral antigen, tumor & even self Ag) are presented in association with MHC class I .
- Exogenous antigens (extra cellular organisms toxins ,soluble proteins) are presented by APC in association with MHC class II .


Virus
(immunogen)
APC
APC (antigen-presenting cell), e.g., macrophage or dendritic cell
Class II MHC protein
Antigen processing within macrophage; viral proteins cleaved into small peptides
IL-1
APC
Helper T cell
CD4
Viral epitope
T-cell receptor for Ag (TCR)
Activation of helper T cell
TCR
IL-2 receptor
Helper T cell
IL-4 (BCGF)
IL-5 (BCDF)
Activation of B cell
IgM monomer
IL-2
CD4
Activation of cytotoxic T cell
IL-2
B cell
Cytotoxins
Viral epitope
Cytotoxic T cell
IL2-R
TCR
CD4
Memory TH cell
Virus (immunogen)
CD8
Cell death
Differentiation
Class I MHC protein
Virus-infected cell
TCR
CD8
Memory TC cell
Memory B cell
Plasma cell

Major Histocompatibility Complex (MHC) or Human Leukocyte Antigen (HLA)

Class I molecules
Found on all nucleated cells

Class II molecules
Found on dendritic cells, macrophages, B cells



Pr. Jean Dausset
Nobel prize
1980

Clinical problems with MHC molecules

- **Major causes for organ transplant rejection**
  - HLA molecules mismatch between donor and recipient (Allograft)
  - Graft-Versus-Host reaction (GVH)

- **HLA association and autoimmune disease**
  - Ankylosing spondylitis
    - HLA-B27 -> 90% of patients
  - Insulin-Dependent Diabetes Mellitus
    - HLADQ2 -> 50-75% of patients

Lymphocytes :

1. Thymus derived cells : (T - cell).

Originate from stem cell in Bone Marrow but mature in thymus

2. Bone marrow - derived cell : (B cell).

Originate & mature in bone marrow

3. Natural killer cells

1.T lymphocyte:

T-cell maturation

- **The main two process of maturation involved :**

A- positive selection :

- **T-cell that recognize foreign antigen via MHC will survive.**

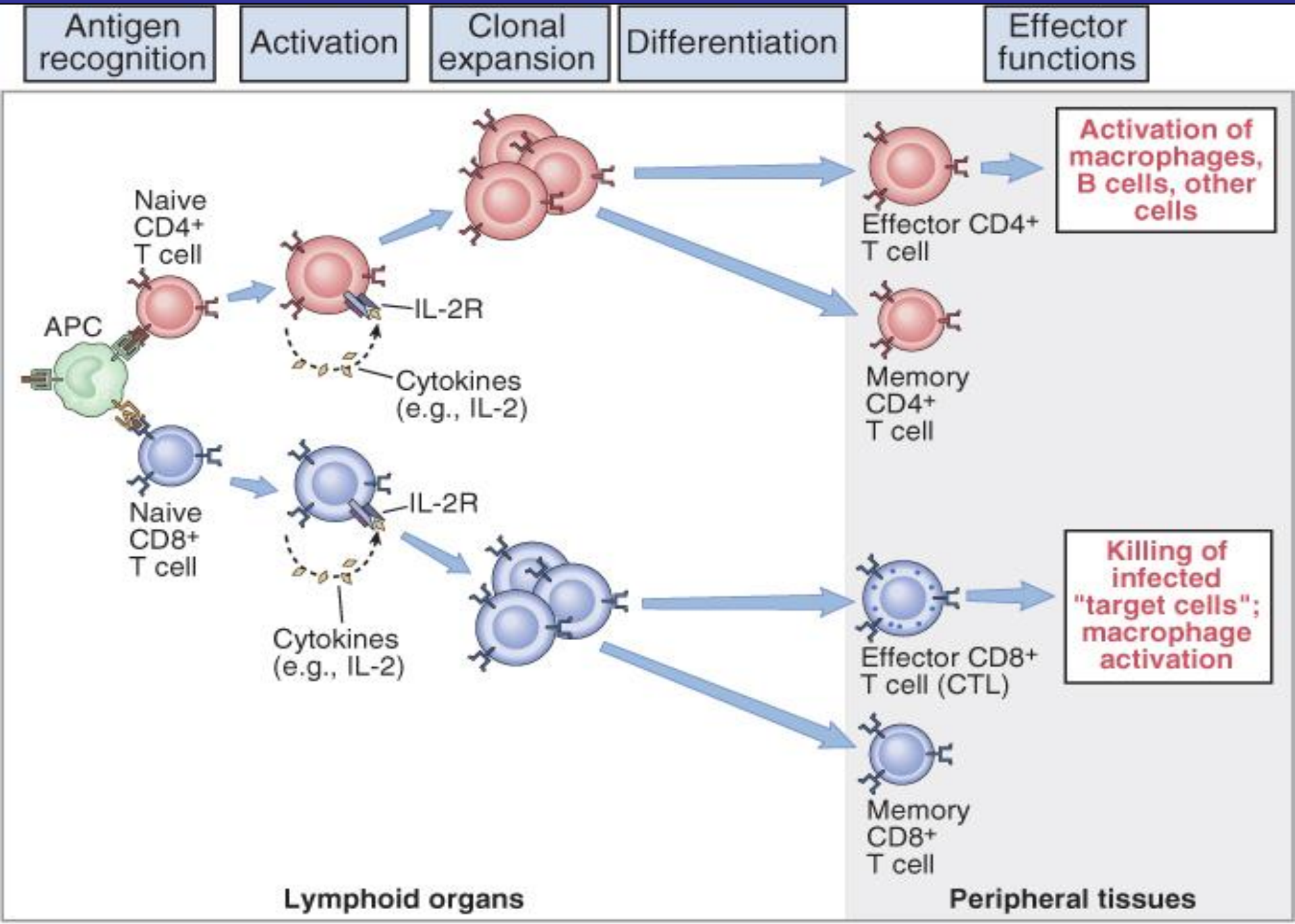
B- Negative selection (Deletion)

- **T-cells with receptor recognize self antigen with high affinity deleted .**

T-cell express either CD4 or CD8 Surface marker which can be used to define the major sub population of T-cell:

1. CD4 characterize the helper T-cell population and produce cytokine and coordinate of immune response.it is called helper because it help B cells and other T cells to multiply & differentiated in to effector cells.

T helper(CD4) recognize Ag associated with MHC II molecules which processed and presented by APC , after Ag recognition CD4 activated
and further subdivided in to TH1,TH2,TH17 and T reg cell based on their cytokines and functional activity.



Phases of T cell responses

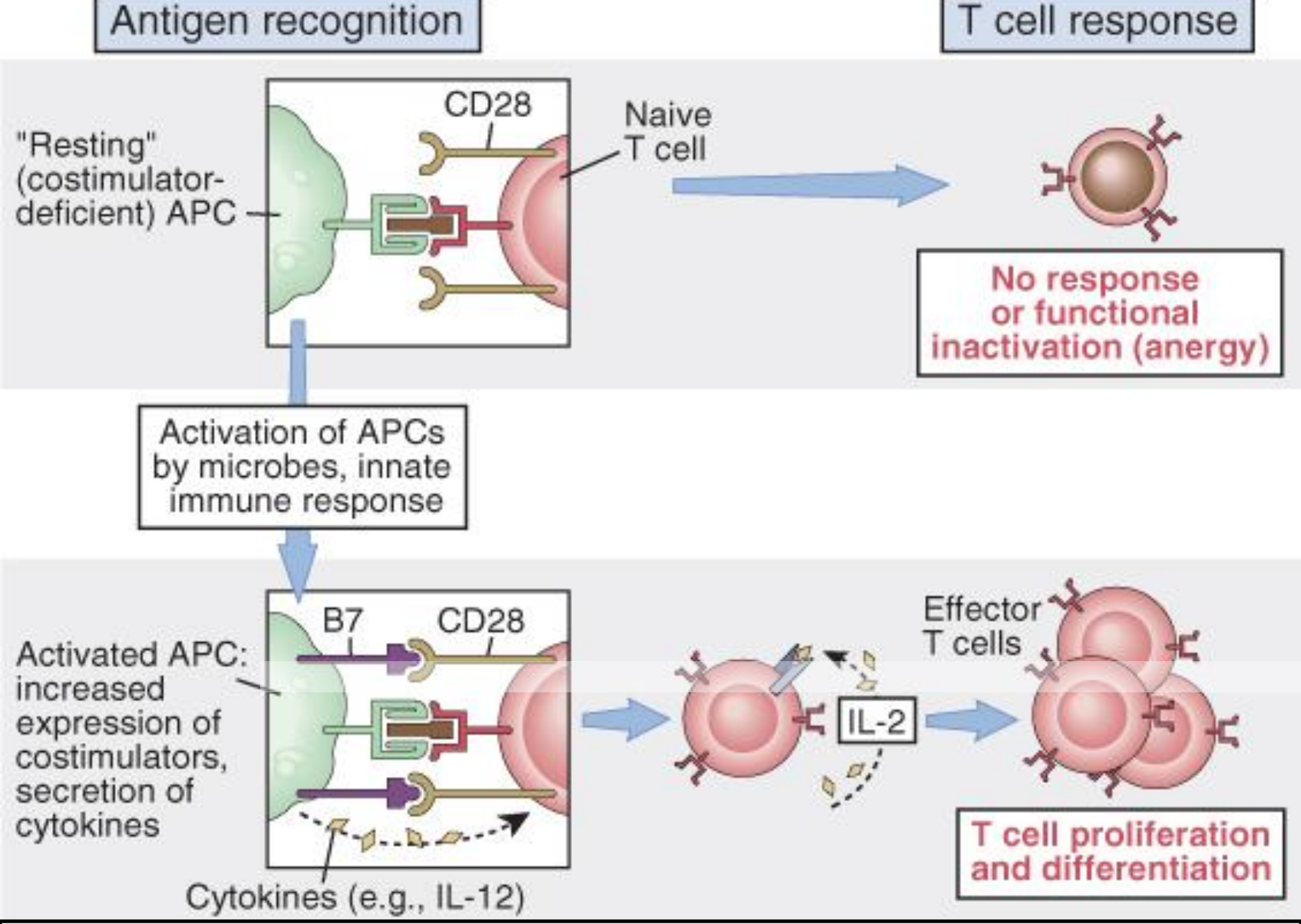
There are three phases

- Antigen recognition phase
- Activation and differentiation phase
- Effector phase

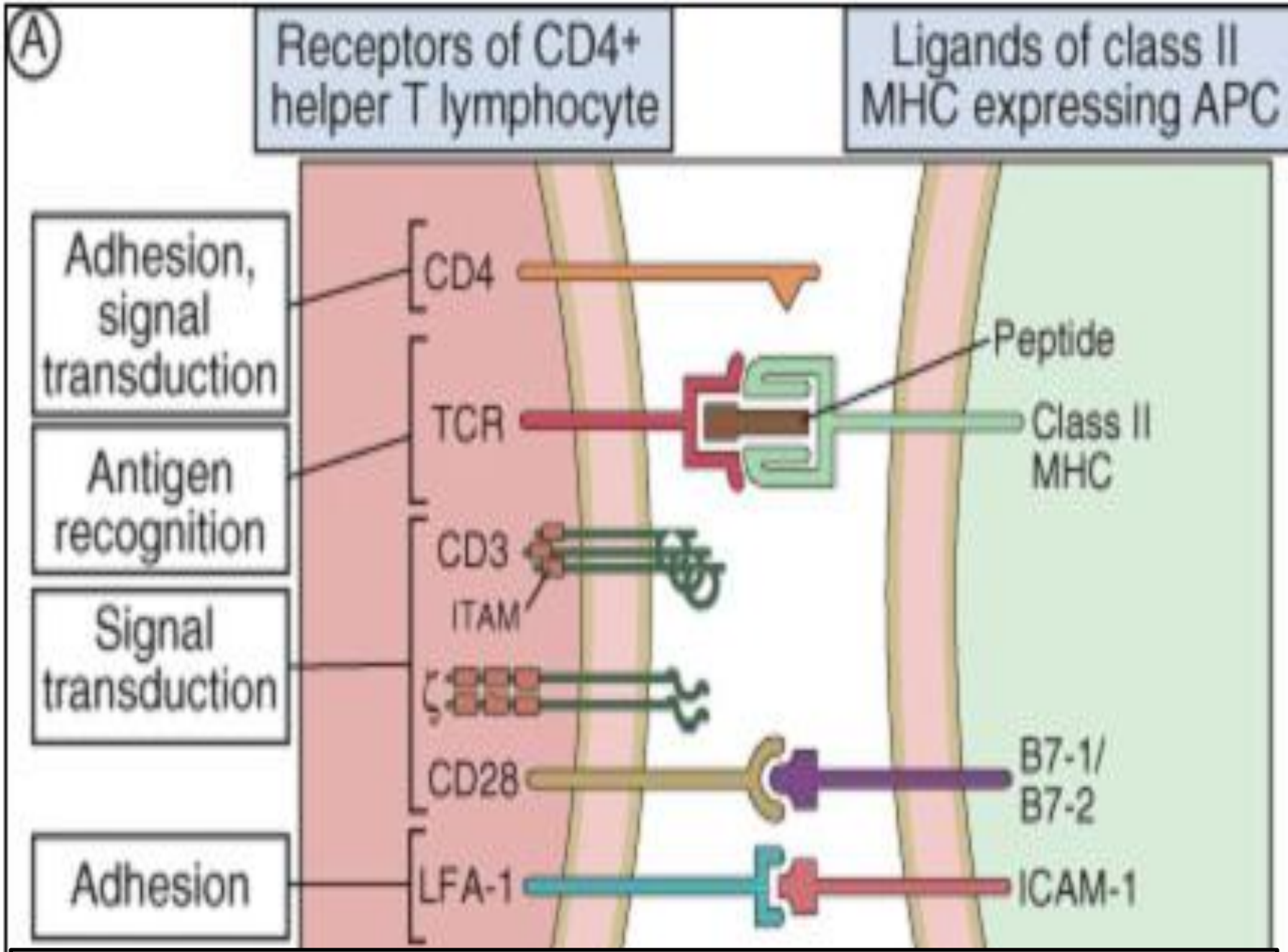
Steps in the activation of T lymphocytes.

Naive T cells recognize major histocompatibility complex (MHC)-associated peptide antigens displayed on antigen-presenting cells (APCs) and other signals . The T cells respond by producing cytokines, such as IL-2, and expressing receptors for these cytokines, leading to an autocrine pathway of cell proliferation. The result is clonal expansion of the T cells.

Some of the progeny differentiate into (1) effector cells, which serve various functions in cell-mediated immunity, and (2) memory cells, which survive for long periods.



The role of costimulation in T cell activation (A)



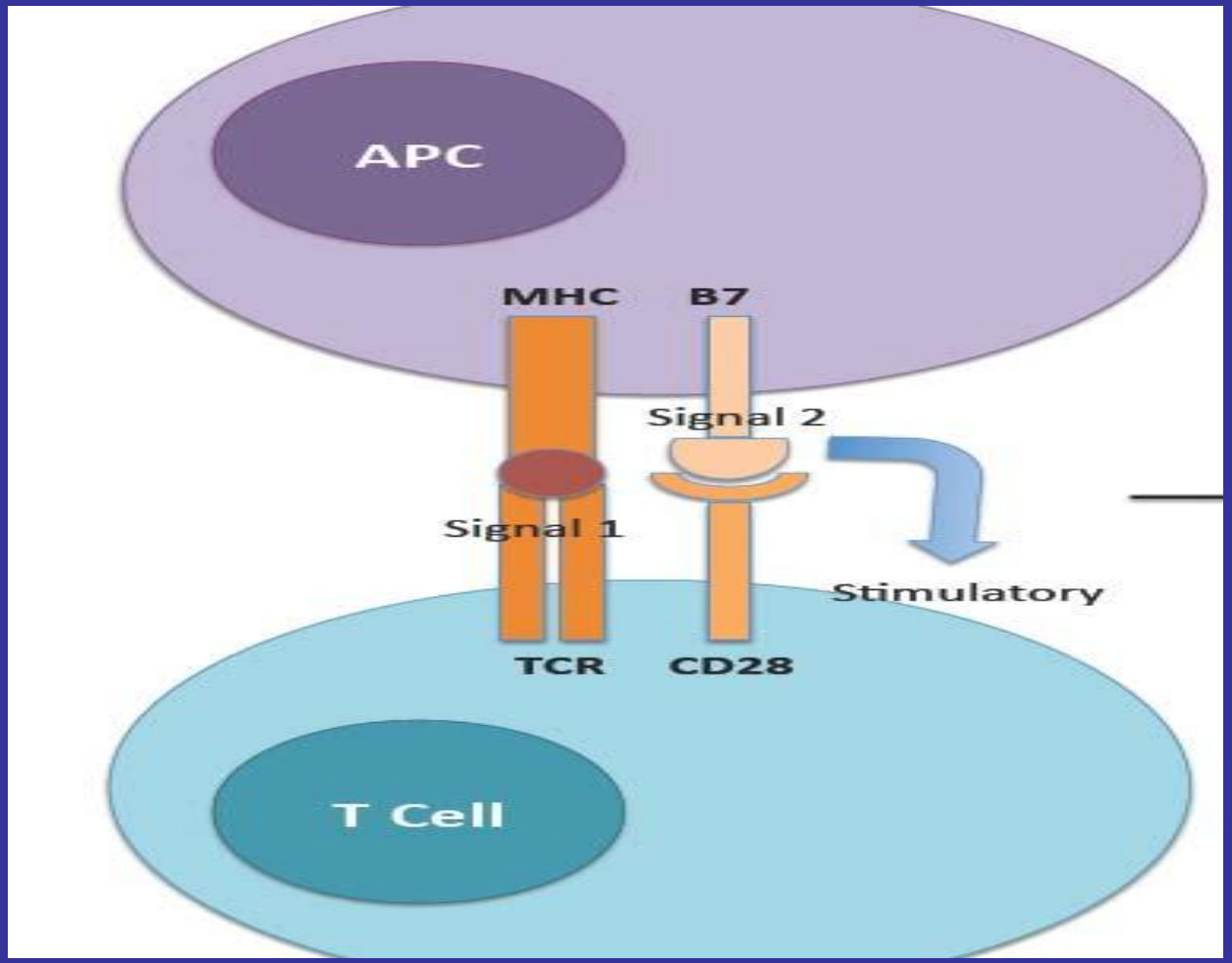
Ligand-receptor pairs involved in T cell activation

ROLE OF COSTIMULATION IN T CELL ACTIVATION, 2ND SIGNAL

The best-defined costimulators for T cells are two related proteins called B7-1 (CD80) and B7-2 (CD86), both of which are expressed on APCs and whose expression is greatly increased when the APCs encounter microbes. These B7 proteins are recognized by a receptor called CD28, which is expressed on virtually all T cells. Signals from CD28 on T cells binding to B7 on APCs work together with signals generated by binding of the TCR and coreceptor to peptide-MHC complexes on the same APCs.

CD28-mediated signaling is essential for initiating the responses of naive T cells; in the absence of CD28-B7 interactions, engagement of the TCR alone is unable to activate the T cells. The requirement for costimulation ensures that naive T lymphocytes are activated fully by microbial antigens, and not by harmless foreign substances, because, as stated previously, microbes stimulate the expression of B7 costimulators on APCs.

ROLE OF COSTIMULATION IN T CELL ACTIVATION, 2ND SIGNAL



Signal transduction in T cell activation

On recognition of Ag and costimulators, T cells express proteins that are involved in proliferation, differentiation and effector functions of the cells.

The biochemical pathways that link Ag recognition with T cell responses consist of the activation of the enzymes, recruitment of adapter proteins, and production of active transcription factors.

The biochemical signals triggered in T cells by antigen recognition and costimulation result in the activation of various transcription factors that stimulate the expression of

1-genes encoding cytokines: Activated T cells can produce cytokines (IL-2, 4, 5, 10,13,17 etc.) and express cytokine receptors, that promote T cells to proliferate and differentiate

2-cytokine receptors

3-Adhesion molecule(LFA-1)

.

Effector functions of activated T cells

1) $CD4^+$ T cells

Th1: secrete IFN-γ, etc. } **Activate macrophages**

express CD40L

effect on lymphocytes: IL-2

effect on neutrophil: TNF-α,β

Th2: IL4,5 Which promote B cell growth and Ig production.

The development of TH1, TH2, and TH17 subsets is not a random process but is regulated by the stimuli that naive CD4+ T cells receive when they encounter microbial antigens.

Cytokines that induce TH1 development include IL-12 (and IL-18), which are produced by microbe-activated antigen-presenting cells (APCs), such as dendritic cells and macrophages.

Interferon-©(IFN-©) made by natural killer (NK) cells or by the responding T cells themselves also is critical for TH1 development. TH2 cells are induced by IL-4, which may be produced by the T cells themselves and by other cells, such as mast cells. TH17 differentiation is triggered by TGF-β which can be made by many cell types, in the presence of inflammatory cytokines such as IL-6, IL-1, and IL-23, which may be produced by APCs also induce Th17 differentiation of T-cell.

$CD8^+$ T cells

Cytotoxicity: kill target cells

a. necrosis: perforin and granzyme

b. apoptosis: granzyme, FasL

Characteristics of $CD8^+$ T cell cytotoxicity

a. Specificity

b. MHC I restriction

c. High efficiency

Generation of memory T cells

1) wandering

2) Long-lived memory to specific antigen

3) Mediate faster, stronger and more effective immune response

- CD8 represent cytotoxic T-lymphocyte (CTL)
- CD8 kill cell infected with intracellular pathogen (bacteria , protozoa, virus).
- CD8 cells recognize and proliferate in response to Ag associated with class 1 MHC, it become effector cells that kill infected cell by that pathogen.

Note:

All T-cell express a surface molecule called CD3 .
CD3 surface marker is specific for T-cell and used to characterize T-cells .

Summary : Features of T lymphocytes

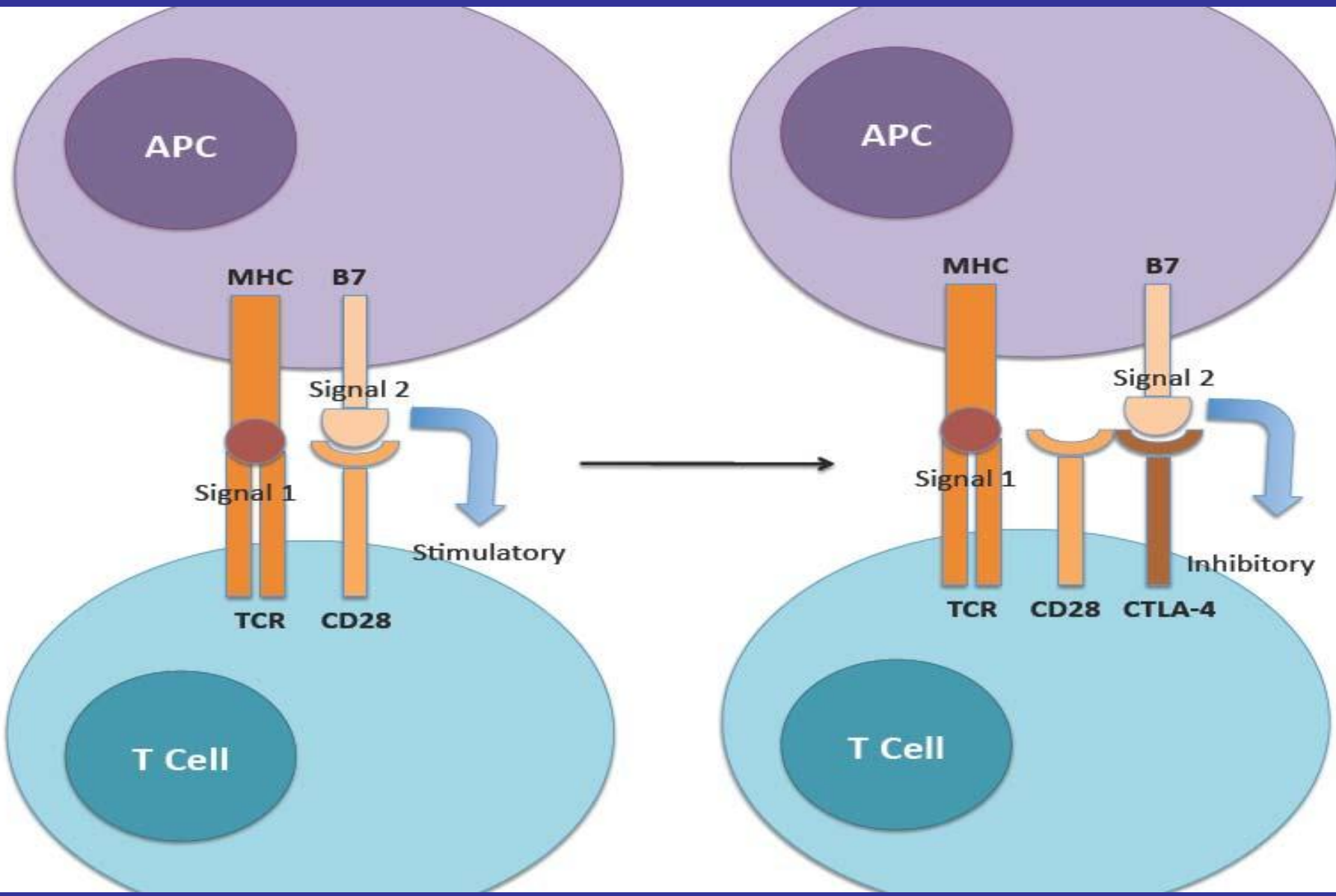
	T cells
Site of maturation	Thymus
Antigen receptor	T cell Receptor
TCR diversity	**Gene rearrangement**
Types of T cells	CD3+ CD4+((TH1-TH2-TH17 cells) CD3+ CD8+ (cytotoxic T cells, CTL)
Memory cells	Yes
Cytokine production	CD4+ TH1 cells: TNFalpha, IFNgamma CD4+ TH2 cells: IL-4, IL-5, IL-10 CD4+-TH17: IL-17

Inhibition of T-cell activation

1-After T-cells have served their function and infection is resolved a cytotoxic T-lymphocyte antigen-4 (CTLA-4) appear on the T-cell surface displacing CD28 and interact with B7 lead to inhibition of T-cell activation by blocking IL-2 synthesis.

2-Programmed cell death-1(PD-1): is another inhibitory protein on T-cells interact with its ligand on APCs (like Dendritic cells and macrophage lead to inhibition immune response

Inhibition of T-cell activation

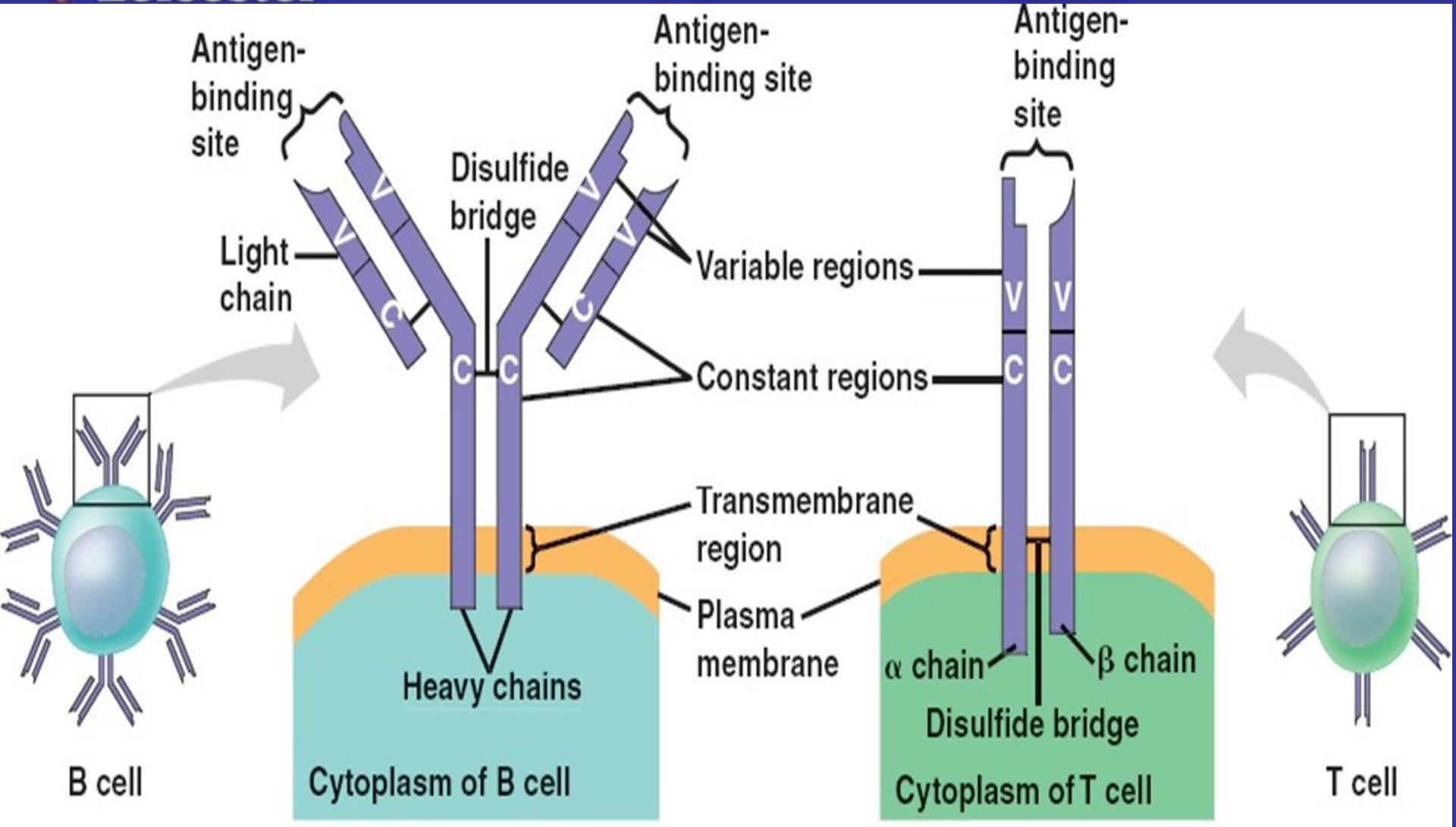


B lymphocyte:

Mature B cells(plasma cell) synthesize immunoglobulin molecules that are found within the cells to be secreted on need or displayed on their surface.

On the surface they function as B cell epitope-specific receptor(BCR)

What are differences between TCR & BCR?



(a) A B cell receptor consists of two identical heavy chains and two identical light chains linked by several disulfide bridges.

(b) A T cell receptor consists of one α chain and one β chain linked by a disulfide bridge.

Immune functions of Antibodies

IgG

1-Ab-dependent phagocytosis
2-Complement activation
3-Neonatal Immunity
4-Toxin/virus neutralization

IgE

1-mmunity against helminths
2-Mast cell degranulation (allergies)

IgA

Mucosal Immunity by Prevent adhesion

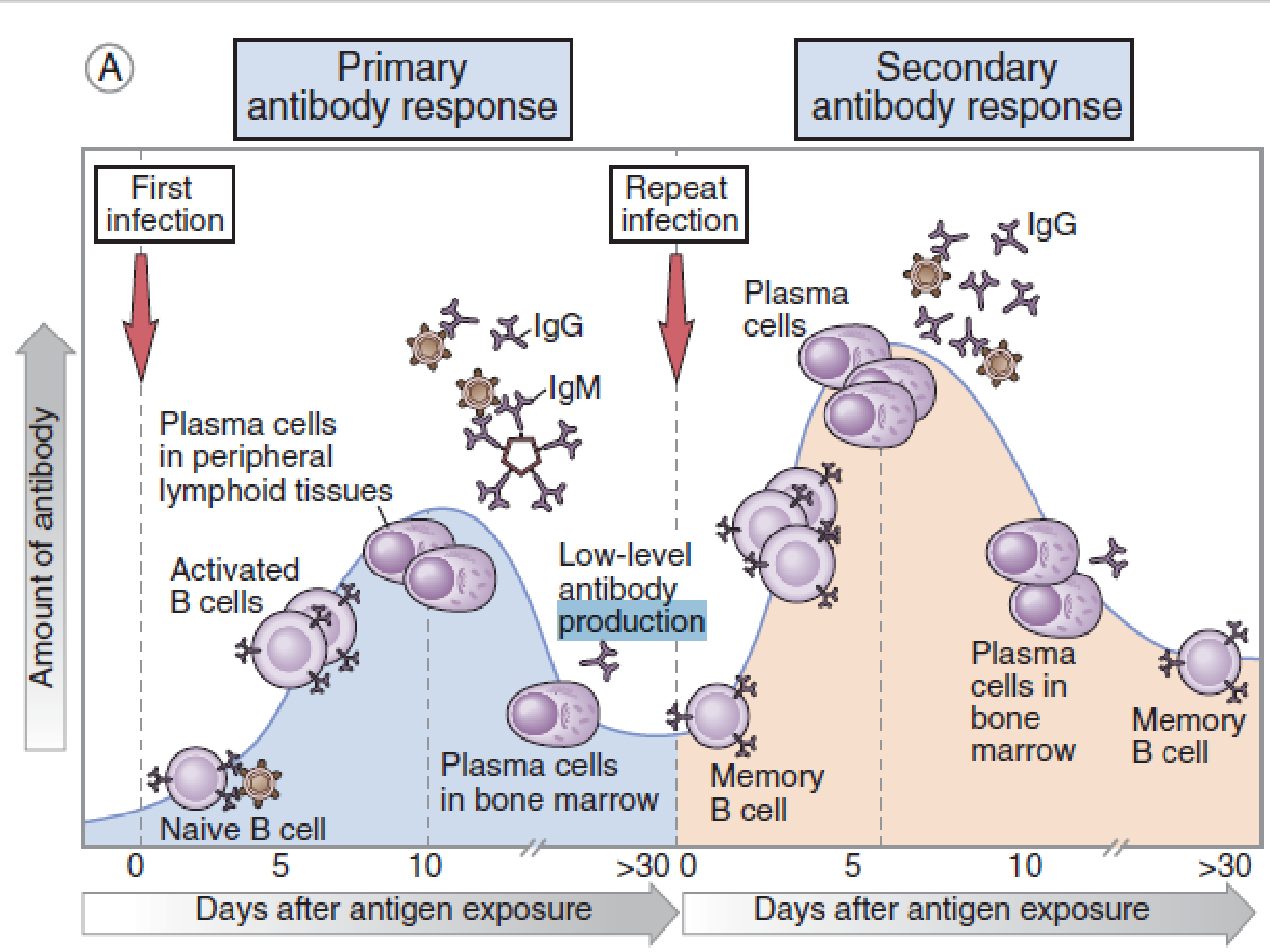
IgM

1-Monemer: as BCR
2-Pentamer: may achieves neutralization, Complement activation

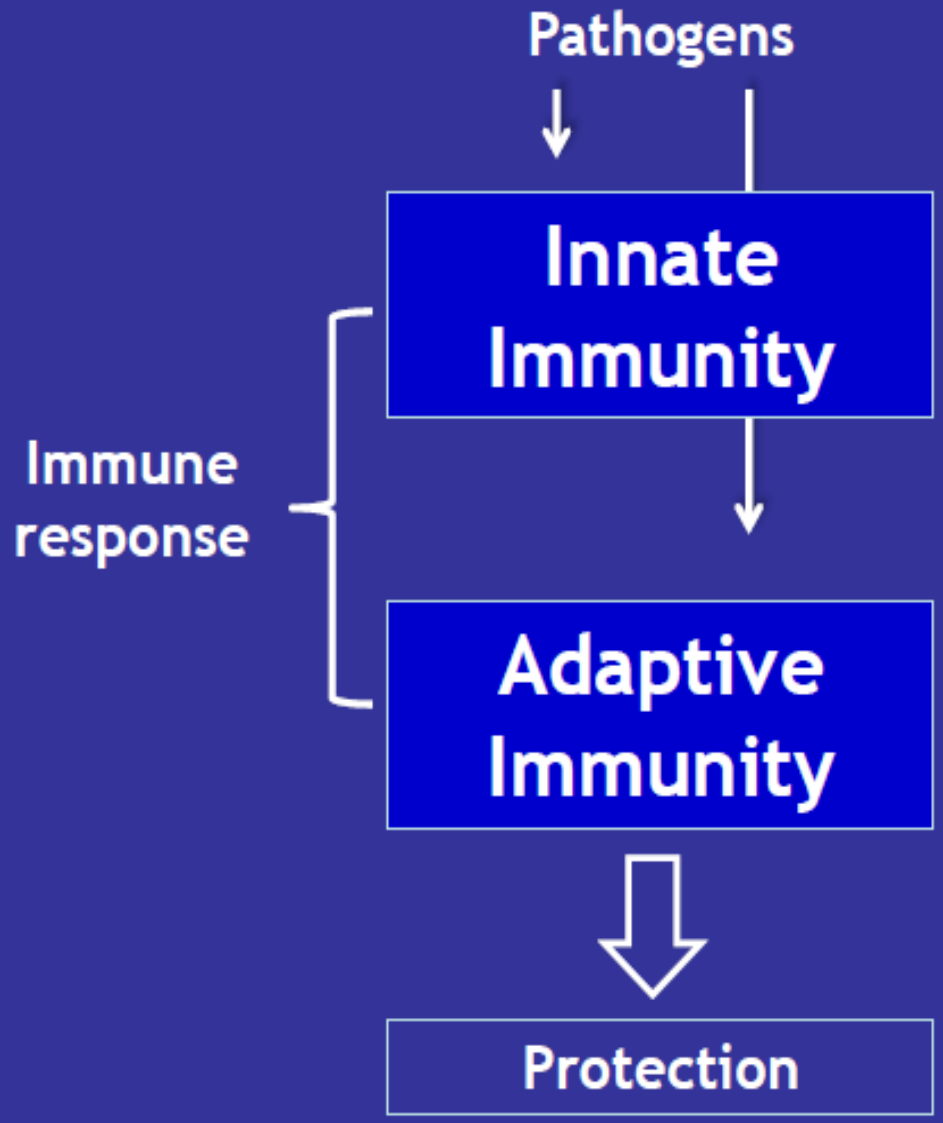
Characteristics of the antibody response (adaptive immunity)

B	Primary response	Secondary response
Lag after immunization	Usually 5-10 days	Usually 1-3 days
Peak response	Smaller	Larger
Antibody isotype	Usually IgM>IgG	Relative increase in IgG and, under certain situations, in IgA or IgE (heavy chain isotype switching)
Antibody affinity	Lower average affinity, more variable	Higher average affinity (affinity maturation)

FIGURE 7-3 **Features of primary and secondary antibody responses.** Primary and secondary antibody responses differ in several respects, illustrated schematically in **A** and summarized in **B**. In a primary response, naive B cells in peripheral lymphoid tissues are activated to proliferate and differentiate into antibody-secreting cells and memory cells. Some antibody-secreting plasma cells may migrate to and survive in the bone marrow for long periods. In a secondary response, memory B cells are activated to produce larger amounts of antibodies, often with more heavy chain class switching and affinity maturation. Many of the features of secondary responses (e.g., heavy chain isotype switching, affinity maturation) are seen mainly in responses to protein antigens, because these changes in B cells are stimulated by helper T cells and only proteins activate T cells. The kinetics of the responses may vary with different antigens and types of immunization. Ig, immunoglobulin.


A
Primary antibody response
Secondary antibody response
First infection
Repeat infection
Amount of antibody
IgG
IgM
Plasma cells in peripheral lymphoid tissues
Activated B cells
Naive B cell
Plasma cells in bone marrow
Low-level antibody production
Memory B cell
Plasma cells
IgG
Plasma cells in bone marrow
Memory B cell
0
5
10
>30
0
5
10
>30
Days after antigen exposure
Days after antigen exposure

The immune response



Immediate protection

- Fast (within seconds)
- Lack of specificity
- Lack of memory
- No change in intensity

Long lasting protection

- Slow (days)
- Specificity
- Immunologic memory
- Changes in intensity

Human survival